

Subcutaneous Purgatives

A Clinical Study on Phenoltetrachlorophthalein

L. G. ROWNTREE

BALTIMORE

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A CLINICAL STUDY ON PHENOLTETRACHLORPHTHALEIN *

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Since the introduction of the hypodermic needle by Alexander Wood of Edinburgh in 1853, a constant and growing tendency to rely more and more on the subcutaneous method of administering drugs has existed because of the fact that this method insures more complete and more rapid absorption and more accurate dosage.

Medicine stands in need of a subcutaneous purgative. The physician and surgeon alike have recognized its necessity. Pharmacologists and experimental therapeutists have repeatedly attempted to supply this demand, turning successively to the salines, to the vegetable purgatives, and to the alkaloids. But still the need is felt, for no preparation suggested has as yet fulfilled the numerous requirements demanded of it. Such a body must act on the intestinal tract and on the intestinal tract only without any untoward effect on any other organ or system, must act with certainty, must be readily soluble, preferably in water, in order that the amount of fluid to be injected may be small, and it must be non-irritant locally. As a rule it should produce its effect within a short time, although in some conditions an action delayed in onset but prolonged in character is to be preferred.

In this connection it is interesting to review the literature dealing with the subcutaneous and intravenous administration of the saline purgatives. Aubert¹ stated in 1851 that intravenous injections of sodium sulphate

* From the pharmacologic laboratory of the Johns Hopkins University and the medical clinic of the Johns Hopkins Hospital.

* Read in the Section on Pharmacology and Therapeutics of the American Medical Association, at the Sixtieth Annual Session, held at Atlantic City, June, 1909.

1. Ztschr. f. rat. Med., 1852, II, 225.

produce purgative effects. Claude Bernard² made a similar statement in 1857 and Headland³ in 1859, though neither of the last writers gave any experimental proof for his claim. Buchheim,⁴ Wagner,⁵ and Hay⁶ concluded, after a considerable amount of experimentation, that sodium sulphate exerts no purgative action if given intravenously or subcutaneously, and this has been the conclusion of practically all investigators in this field until the appearance of a paper by J. B. MacCallum,⁷ which created a new interest in this subject.

MacCallum introduced solutions of the various salines into the veins or under the skin of rabbits, and then studied the effect on movements of the intestines either by observing the movements of intestines through the opened abdominal wall or by observations made on these animals confined in separate metabolism cages. He concluded that all those salts which act as purgatives when introduced into the stomach or intestines have the same action when injected subcutaneously or intravenously. He also stated that barium chlorid possesses this purgative property to the greatest degree, but all of the other salines possess it to a less degree, that the purgative effect is produced by increased secretion as well as increased peristalsis, and that the purgative effect can be counteracted or abolished by calcium chlorid.

Auer⁸ investigated in the same field, but could not obtain MacCallum's results, and claimed that in his experiments sodium citrate used intravenously caused constipation, while magnesium sulphate inhibited intestinal movements.

Bancroft⁹ repeated MacCallum's work and stated that sodium citrate or barium chlorid subcutaneously and sodium sulphate intravenously act as purgatives, but that it is easier to produce fluid feces by administering sodium sulphate or sodium citrate by mouth.

Eckardt¹⁰ gives an excellent review of the work done in this field up to 1905 and presents also the results of his own experiments, which conclusively prove that the

2. *Substances Toxiques et Medicamenteuses*, 1857, p. 85.

3. *Action of Medicines*, 1859, p. 459.

4. *Arch. f. physiol. Heilkunde*, 1854, xiii, 217.

5. *Inaug. Diss.*, Dorpat, 1853.

6. *Jour. Anat. and Physiol.*, xvi, 243.

7. *Am. Jour. Physiol.*, x, 101.

8. *Am. Jour. Physiol.*, xvii, 15.

9. *Jour. Biol. Chem.*, iii, 191.

10. *Inaug. Diss.*, Giessen, 1905.

salines will not furnish us the sought-for subcutaneous purgative.

Although these investigations are of academic and scientific interest, they help to throw some light on the method of action of salines, and, although intestinal peristalsis is undoubtedly increased by some at least of these salts, yet the increase in activity is not sufficiently marked to result in purgation unless toxic or lethal doses are injected. The salines, therefore, are of no practical importance to medicine as subcutaneous purgatives.

Barium chlorid, however, will produce purgation administered either subcutaneously or intravenously, and it is frequently used as such by veterinarians, 1 gm. being sufficient to purge a horse weighing 1,000 pounds. But barium is the most poisonous of the alkaline earths and it affects many organs. It accelerates the heart, enormously raises blood-pressure, and in large doses, besides purging, causes vomiting and sometimes tonic and chronic convulsions. The widespread nature of its activity and its toxicity preclude its general adoption in this field.

VEGETABLE PURGATIVES ADMINISTERED SUBCUTANEOUSLY

Similar investigations have been carried on with the vegetable purgatives, aloes,¹¹ colocynth and cathartine acid having been tested. Hiller¹² regards colocynthin as the most suitable for this purpose. No doubt can exist as to their efficacy when so used, but all these bodies are strongly irritant and the local reaction at the point of injection is frequently extremely severe. They cannot be used in this way except in very exceptional instances where the indications are imperative, and then only with a grave possibility of sloughing occurring at the point of injection.

An effort was made to see if croton oil greatly diluted could be used subcutaneously. Two drops of croton oil were added to 5 c.c. of olive oil and under aseptic precautions introduced beneath the skin of a dog. On the following day a painful swelling was found at the point of injection. This increased in size, became very tender, and persisted for several days. No evidence of an action on the intestine was noted until the fifth day, when a large amount (100 gm.) of fluid feces was passed. The

11. Hans Meyer: Arch. f. exper. Path., xxviii, 186.

12. Ztschr. f. klin. Med., iv, 480.

stools remained soft for three days and then returned to a normal consistency.

An experiment with castor oil yielded a very similar result. A dog was injected with 25 c.c. of sterile castor oil on December 12. No purgative effect was obtained until December 18, but this was so slight in degree that it was doubtful. A large painful swelling occurred at the point of injection, which persisted until December 21. It is scarcely possible that any serviceable subcutaneous purgative will be obtained from this class of drugs.

APOCODEIN

The work done with apocodein, however, has been more fruitful. This is an alkaloid corresponding in derivation to apomorphin from morphin, obtained by dehydrating codein. It was first carefully studied by Guinard.¹³ He noted that it produced no nausea or vomiting, and following its administration he observed the increased peristalsis through an open abdominal wall. Murrel¹⁴ used it as an expectorant in 1891, Toy¹⁵ as a sedative in maniacal cases in 1895. Combemale¹⁶ introduced it as a purgative by mouth in 1900. He interested Raviart and Barton,¹⁷ who in the same year administered it subcutaneously in 34 cases of constipation with very encouraging results. Giraud,¹⁸ 1903, used it in 8 cases of constipation, also with satisfactory results. In the same year Heinze¹⁹ tested it in a series of 30 cases of constipation. He had 47 per cent. of successful cases and in 53 per cent. it utterly failed. From his experience he concludes that apocodein is unsatisfactory in that it is uncertain in action, but admits that it works very well in many instances.

The dose of this drug is small, .02 gm. of the hydrochlorate being usually sufficient, while .05 gm. is the maximal dose. Most of the writers claim that the first evacuation follows shortly after the administration of the injection, frequently within one to two hours. Heinze, however, states that the average time is from ten to twelve hours.

13. Lyon méd., 1893, pp. 21 and 23.

14. Brit. Med. Jour., 1891, i, 455.

15. Semaine méd., 1895, p. 346.

16. Semaine méd., 1900, p. 422.

17. Echo méd. du nord, December, 1902.

18. Thèse de Lyon, 1903.

19. Psychiat.-Neurol. Wehnschr., 1903-4, v, 297.

The objections to apocodein are worthy of consideration, for it certainly does not represent the ideal subcutaneous purgative as outlined above. According to Dixon²⁰ it lowers the blood pressure, dilates the arterioles, increases peristalsis by its sedative action on the inhibitory ganglia of the sympathetic system, increases the rate of the heart beat, and increases nerve reflexes. Its actions are too numerous and complex and involve too many symptoms. Unfortunately, although readily soluble in water, it is irritant, locally, many of the patients having complained of pain and an abscess having followed its use in one case. Its action is also short in duration, constipation usually returning in a day or two.

Notwithstanding these drawbacks apocodein is, however, a serviceable hypodermic purgative. Personal experience has been limited to animal experimentation. On one occasion an evacuation of the bowels followed within an hour of the injection of 0.04 gm. subcutaneously in a dog. In other instances movements occurred within ten or twelve hours, but the stools were not soft and no prolonged action was obtained.

ESERIN

Eserin or physostigmin has also been investigated. Dickerhoff²¹ first suggested its use, and since then it has been tried clinically by many investigators, von Noorden,²² Packard,²³ Pankow,²⁴ Craig,²⁵ Jewett,²⁶ particularly by surgeons and obstetricians. It is not given solely for its purgative effect but most frequently to prevent or overcome intestinal paresis following surgical operations, or to overcome intestinal atony following parturition, or to expel gas from a distended intestine. Craig has used it extensively, and he administers it immediately after opening the abdomen provided no contraindication presents itself. He claims that it is of more value in preventing or warding off threatened intestinal paresis than it is in curing this condition when once established. He advises large doses, 1/35 gr. of

20. Jour. Physiol., xxx, 97.

21. Wehnschr. f. Thierh. u. Viehz., 1882, xxxvi, 309.

22. von Noorden; Berl. klin. Wehnschr., 1901, p. 1057.

23. Philadelphia Med. Jour., May 24, 1902.

24. Zentralbl. f. Gyn., June, 1904.

25. Am. Jour. Obst., April, 1904. Am. Jour. Obst., September, 1904. New York Med. Jour., 1905, lxxxv, 527.

26. Brooklyn Med. Jour., xlx, 42.

the acetate administered early subcutaneously, and he regards this as essential for successful results, attributing Pankow's lack of results to the smallness of the dose utilized. Jewett's results confirm those of Craig. But all these authors find that though preventing paresis eserin is not always sufficient to produce purgation, thus rendering necessary the administration of other purgatives by mouth.

Eserin is an exceedingly powerful alkaloid and must be handled judiciously. Undoubtedly it has its place when used in conditions described above, but it is not of wide practical application and will never come into general use alone as a subcutaneous purgative.

SODOPHTHALYL

Fleig²⁷ in a recent publication states that he has prepared a soluble salt of phenolphthalein which he has named sodophthaly, and which according to his account is being used successfully as a hypodermic purgative in the clinics in Montpellier. His account of the mode of preparation and of the chemical properties of this derivative are so exceedingly meager that no definite idea of its chemical constitution can be formed. I assume here that it is the disodium salt of phenolphthalein which has also been described by Meyer and Marx,²⁸ and which is made by the addition of sodium hydroxid to phenolphthalein. This salt is very soluble, and, being a combination of a very weak acid with a very strong base, it is readily hydrolizable and acts like a solution of the alkali itself; that is, it is decidedly irritant.²⁹ It is with great interest that we await the report of the therapeutic application of sodophthaly in the clinics of Montpellier; and if this substance is identical with the disodium salt of phenolphthalein, it is difficult to see how it can be used on account of its irritating effect at the point of injection.

In April, 1908, Abel and Rowntree³⁰ started an investigation of the phthalein group with particular refer-

27. Arch. internat. de pharmacod. et de therap., xviii, 327.

28. Ber. d. deutsch. chem. Gesellsch., 1908, xli, 2446.

29. In animal experiments Abel and Rowntree used the disodium salts of both phenolphthalein and its tetrachlor derivative for injecting subcutaneously in dogs. Irritation, infiltration, and sterile abscesses followed in many of the animals so that these preparations were abandoned.

30. Abel and Rowntree: Jour. Pharmacol and Exper. Therap. 1909, I, 231.

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ence to the excretion, the absorption, and the purgative action of different members of this family, and also as to the effect of substitution of different parts of the phthalein radicle on the pharmacologic action of the drug.

It was proved that olive oil when heated would dissolve phenolphthalein and many of its derivatives, and that this oil preparation possessed some value as a purgative when injected beneath the skin of dogs. But it was soon observed that more prolonged purgative action was obtained when phenoltetrachlorphthalein was employed than when any other phthalein at their command was used.

METHOD OF PREPARING OIL SOLUTION

The solution of phenoltetrachlorphthalein employed throughout this investigation is prepared in the following way: Neutral olive oil is slowly heated to 210 C., and when this temperature is reached finely powdered phenoltetrachlorphthalein is added with stirring. The heating is continued for not longer than five minutes and the temperature is not allowed to exceed 220 C. In order to remove any traces of foreign matter or undissolved phthalein, the oil solution is filtered hot into sterilized flasks and set aside for use. Olive oil thus treated will dissolve the chlor body to the extent of about 0.2 gm. to every 10 c.c. of oil, while it will dissolve phenolphthalein itself to a slightly greater extent at a slightly lower temperature.

Analytical experiments were made which show that no appreciable saponification of the oil takes place during this procedure. Nevertheless, in order to lessen the risk of saponification, the custom was adopted of preparing only 40 c.c. of such a solution at a time, though doubtless larger volumes of the solution might be prepared at one operation.

Phenolphthalein exhibits a greater tendency to come down out of such a solution, but a properly prepared solution of the chlor body will stand some days without any precipitation whatever.

ABSORPTION, EXCRETION AND MODE OF ACTION

Before entering on the report of the clinical application of this substance a few words concerning its absorption, its fate in the body, its channels of excretion and its mode of action will not be out of place.

Practically all the drug is absorbed from the local seat of injection into the general circulation in from sixteen to twenty-four hours. It appears in the bile in the conjugated form, and later in both the free and conjugated condition, and continues to be excreted in the bile of a biliary fistula dog for from forty-eight to seventy-two hours and in the feces of a normal dog as long as five and six days. Part of the drug is re-absorbed again from the large intestines, and the purgative action produced is consequently very prolonged in nature. No traces of the drug can be detected in the urine; it thus differs from phenolphthalein, which after being injected under the skin escapes to a considerable degree by way of the kidneys.

After a prolonged period of experimentation in a series of forty injections in dogs it was learned that injections of this body in neutral olive oil were not followed by any untoward results either locally at the point of injection or systemically, and that no system other than the alimentary was influenced by this substance. Its introduction into the dispensary and wards of the hospital for further investigation was therefore considered justifiable and advisable. A study to determine its clinical value was accordingly undertaken at the suggestion of Dr. Abel.

ADMINISTRATION TO OBSTETRICAL PATIENTS

The first series of injections were made in the obstetrical wards by the permission of Dr. Williams and with the kind assistance of Dr. Storrs. The cases represent women in the puerperium, some of whom received the injection in place of the usual initial purgative, while others received it when a purgative was indicated later during the lying-in period. This table also includes the result of one injection of 12 c.c. of the oil preparation given to a dispensary patient (No. 3, Mrs. R.). This case is included here because of the smallness of the dose administered.

SUBCUTANEOUS INJECTIONS OF PHENOLTETRACHLOROPHTHALEIN

DOSE.	PATIENT.	Day of injection.	Days following injection.						
			1	2	3	4	5	6	7
Patients receiving 0.2 gm. in 10 c.c. of oil.	1 Mrs. H.		1	0	1	0			
	2 Mrs. A.	1	2	0	0	1			
	3 Mrs. R.		1	1	1	0	1	0	1
Patients receiving 0.3 gm. in 15 c.c. of oil.	4 Mrs. A.		1	2	0	1	2	2	2
	5 Mrs. C.		3	1	0	1	1	0	1
	6 Mrs. F.		0	1	0	1	1		

These results are not entirely satisfactory, but in the light of later experiences this is thought to be due to the fact that the dose administered was too small, and probably had the dose been larger the results would have been correspondingly more favorable. However, a decided laxative effect was obtained. The stools became softer and in some instances semifluid or of the consistency of a porridge, and in one instance contained the drug as late as the fifth day. In none of the cases did local irritation or inflammation follow the injection, nor were griping pains or colic complained of by any patient at any time following the administration. The urine and the milk were collected from the mothers, but no drug could be detected in either secretion.

A glycerin suppository was given at the end of thirty-six hours when necessary for the first movement, and repeated if thirty-six hours again intervened without an evacuation.

RESULTS OF ADMINISTRATION TO DISPENSARY PATIENTS

The results just presented, though not entirely satisfactory, were, however, sufficient to justify a further investigation as to the value of this subcutaneous laxative, particularly in view of the prolonged nature of the action exerted throughout a period of several days.

The patients, indicated on the table presented below, were selected cases of chronic constipation obtained from the medical dispensary of the Johns Hopkins Hospital through the courtesy and assistance of Dr. McCrae and the other members of the dispensary staff. Only male patients were selected in whom the symptom "chronic constipation" constituted the chief cause of complaint. This symptom varied in the different individuals to all degrees of severity, and had persisted for periods varying from weeks to twenty years. Many of the patients had been returning to the clinic for months or years, never having a bowel movement without resorting to drugs. Some responded well to daily doses of cascara, to pills, or to various forms of teas, while others had derived little or no benefit from any form of previous treatment.

Under aseptic precautions each of these patients was given 0.4 gm. of phenoltetrachlorophthalein, 20 c.c. of the freshly prepared oil preparation, subcutaneously in the gluteal region. Each one was also supplied with two glycerin suppositories and was asked to follow these

rules: (1) Drink water freely; (2) eat some fruit each day; (3) take walking exercise every day; (4) go to toilet night and morning and stay five to ten minutes if necessary; (5) use a glycerin suppository at the expiration of thirty-six hours if the bowels have not moved, and use the other suppository later if thirty-six hours again pass without an evacuation.

PATIENTS RECEIVING 0.4 GM. OR 20 C.C. OF OIL PREPARATION

Patient.	Day of injection.	Days following injection.							2d week.	3d week.	Final result.
		1	2	3	4	5	6	7			
7 M. K.	..	1	1	1	0	1	1	..	..	..	Constipation returned.
8 H. C.	1	1	2	1	1	1	1	1	4	3	Constipation returned.
9 J. C.	..	1	2	1	2	1	1	2	7	7	No return of constipation.*
10 I. B.	..	1	0	1	1	1	2	1	8	7	No return of constipation.*
11 J. S.	..	1	1	1	1	2	1	1	4	3	Constipation returned.
12 H. G.	1	2	2	3	2	2	2	1	7	7	No return of constipation.*
13 J. L.	..	0	0	0	..	..	..	..	..	..	No effect.
14 I. W.	..	1	1	2	0	1	0	1	3	2	Constipation returned.
15 L. L.	..	2	1	0	1	0	1	..	3	3	Constipation returned.
16 J. S.	..	1	1	0	1	1	0	1	12	8	No return of constipation.*
17 L. K.	1	1	0	1	1	1	0	1	6	7	Constipation returned.
18 J. B.	..	3	1	1	1	1	0	1	7	7	No return of constipation.*
19 F. T.	1	1	0	1	1	1	1	1	5	6	No return of constipation.*
20 †	1	2	2	2	2	2	2	0	..	..	Result not known.
21 O. N.	..	1	1	1	1	1	1	1	..	..	Constipation returned.
22 J. W.	1	1	1	1	1	1	1	1	7	7	No return of constipation.*
23 W. H.	..	1	2	2	1	..	..	..	..	..	No return of constipation.*
24 B. W.	1	2	2	3	Took cascara				..	..	Constipation not relieved.
25 L. M.	..	1	1	0	0	..	..	..	..	..	..
26 A. B.	1	2	1	1	1	1	1	2	8	8	No return of constipation.*
27 J. W.	..	2	2	2	2	2	2	1	14	14	Constipation returned.
28 W. B.	..	0	0	0	..	..	..	..	..	..	No effect.
29 W. B.	1	1	1	1	1	1	1	1	7	7	No return of constipation.*
30 J. J.	..	1	1	1	0	0	..	..	..	..	..

* No return of constipation after periods varying from two to six months.

† Dr. Rosenthal's patient.

One of the most striking phenomena revealed by the study of this table is the prolonged nature of the action produced by this drug. It is not claimed that one injection will produce purgation for more than four or five days, but that it will do this, and that without the aid

of psychotherapy, has been proved by numerous experiments on dogs.

It was hoped that the success attending the observance of the hygienic and dietetic rules outlined above, during the period in which daily movements of the bowels were being induced by the chlor body, would encourage the patients to continue in the observance of these rules, and that they would thus obtain a permanent cure without further resort to drugs. This was realized in ten patients out of the twenty-five cases of chronic constipation. That the total results recorded during the first week following injection are not due to psychic, hygienic and dietetic treatment is proved by the fact that many of these same patients were old dispensary cases who had probably had the same suggestions and advice on numerous previous visits as well as by the similar results, already mentioned, which were obtained in animals.

It is very evident that phenoltetrachlorphthalein is not an ideal purgative. Several serious objections at once present themselves:

1. The insolubility of this drug in water.
2. The slight degree of its solubility in oil necessitating a large volume for injection.
3. The long time elapsing before the onset of its laxative action, which appears usually eighteen to twenty-four hours after administration of the drug.
4. The mild character of its action, which is rather laxative than purgative.

At the same time several redeeming features which make this substance of peculiar value must not be overlooked:

1. The prolonged nature of its action.
2. The absence of crampy pains and colic throughout the period of its action.
3. The constancy, at least in the cases so far studied, with which it has produced results.

Phenoltetrachlorphthalein, then, is efficient, non-toxic and non-irritant when administered as a subcutaneous purgative, but its insolubility in water and its low solubility in oil stand in the way of its wide application as such in practical therapeutics but do not detract from its efficiency when a subcutaneous purgative is indicated. It may prove of considerable value in certain conditions, as (a) in coma; (b) in marked gastro-

intestinal irritability which contraindicates the administration of a purgative by mouth; (c) among the insane, who often refuse to take any medicine by mouth and who fight vigorously against the administration of enemata; (d) in certain cases of chronic constipation, combined with hygienic, dietetic and psychic treatment.

Phenoltetrachlorphthalein is worthy of a trial in the field of abdominal surgery, when its introduction beneath the skin can be accomplished during the anesthesia without any pain whatever, where its mild prolonged laxative effect, e. g., a soft daily stool, starting on the day following the operation and continuing for a period of from four to six days, may possibly entirely dispense with the necessity of administering any other purgative by mouth during the first week subsequent to the operation.

